Title: Degradation of the chemotherapy drug 5-fluorouracil on medical-grade silver surfaces

Author: Helene Kjær Risinggård Simon Cooil Federico Mazzola Di Hu Marit Kjærvik Elise Ramleth Østli Nilesh Patil Alexei Preobrajenski D. Andrew Evans Dag W. Breiby Thuat T. Trinh Justin W. Wells

PII: S0169-4332(17)33514-6
DOI: https://doi.org/doi:10.1016/j.apsusc.2017.11.221
Reference: APSUSC 37803

To appear in: *APSUSC*

Received date: 29-8-2017
Revised date: 9-11-2017
Accepted date: 26-11-2017

Please cite this article as: Helene Kjaer Risinggård, Simon Cooil, Federico Mazzola, Di Hu, Marit Kjaervik, Elise Ramleth Ostli, Nilesh Patil, Alexei Preobrajenski, D. Andrew Evans, Dag W. Breiby, Thuat T. Trinh, Justin W. Wells, Degradation of the chemotherapy drug 5-fluorouracil on medical-grade silver surfaces, *<![CDATA[Applied Surface Science]]>* (2017), https://doi.org/10.1016/j.apsusc.2017.11.221

Degradation of the chemotherapy drug 5-Fluorouracil on medical-grade silver surfaces

Helene Kjær Risinggård[a], Simon Cooil[a,c], Federico Mazzola[a,b], Di Hu[c], Marit Kjærvik[f], Elise Ramleth Østli[d], Nilesh Patil[a], Alexei Preobrajenski[e], D. Andrew Evans[c], Dag W. Breiby[a], Thuat T. Trinh[g,h], Justin W. Wells[i]

[a] *Department of Physics, Norwegian University of Science and Technology (NTNU), 7491 Trondheim, Norway*
[b] *School of Physics and Astronomy, University of St. Andrews, United Kingdom*
[c] *Department of Physics, Aberystwyth University, Aberystwyth SY23 3BZ, UK*
[d] *Department of Material Science and Engineering, Norwegian University of Science and Technology (NTNU), 7491 Trondheim, Norway*
[e] *MAX IV, Lund University, Box 118, 22100 Lund, Sweden*
[f] *Dpt 6.1 Surface Analysis and Interfacial Chemistry, Bundesanstalt für Materialforschung und Prufüng, Berlin, Germany*
[g] *Computing and Design Bionanochemistry Research Group, Faculty of Applied Sciences, Ton Duc Thang University, Ho Chi Minh City, Vietnam*
[h] *Department of Civil and Environmental Engineering, Norwegian University of Science and Technology (NTNU), 7491 Trondheim, Norway*
[i] *Center for Quantum Spintronics, Department of Physics, Norwegian University of Science and Technology (NTNU), 7491 Trondheim, Norway*

Abstract

The degradation of the chemotherapy drug 5-Fluorouracil by a non-pristine metal surfaces is studied. Using Density Functional Theory, X-ray Photoelectron Spectroscopy and X-ray Absorption Spectroscopy we show that the drug is entirely degraded by medical-grade silver surfaces, already at body temperature, and that all of the fluorine has left the molecule, presumably as HF. Remarkably, this degradation is even more severe than that reported previously for 5-Fluorouracil on a pristine monocrystalline silver surface (in which case 80% of the drug reacted at body temperature)[1].

We conclude that that the observed reaction is due to a reaction pathway, driven by H to F attraction between molecules on the surface, which results in the direct formation of HF; a pathway which is favoured when competing pathways involving reactive Ag surface sites are made unavailable by environmental contamination. Our measurements indicate that realistically cleaned, non-pristine silver alloys, which are typically used in medical applications, can result in severe degradation of 5-Fluorouracil, with the release of HF – a finding which may have important implications for the handling of chemotherapy drugs.

Keywords: Surface science, Chemotherapy, DFT, Photoemission, Fluorouracil, Silver

*Corresponding author
Email address: : trinhthanhthuat@tdt.edu.vn (Thuat T. Trinh)

1. Introduction

The number of new cancer cases is increasing each year: In 2012, 14.1 million new cases were reported worldwide, and the *World Cancer Report 2014* predicts that the number will be close to 25 million per year in 20 years time [2]. Chemotherapy drugs are one of the important tools in fighting cancer, typically being delivered intravenously using a central venous catheter and metal needles/connections/coatings. The catheters are made from various types of plastic, and may be coated with argentic alloys to prevent them from deteriorating on exposure to drugs and bodily fluids [3, 4]. 5-Fluorouracil (5-Fu) is one of the most commonly used chemotherapy drugs; it is almost identical to the nucleobase uracil, except that a hydrogen atom is replaced by a fluorine atom. 5-Fu disturbs the reproduction of cancer cells by inhibiting DNA replication, ultimately leading to cell death. 5-Fu also has potential for targeting the protein 'Human Epidermal Growth Factor Receptor 2', the over-expression of which is strongly linked certain aggressive forms of breast cancer [5].

The interaction between cancer drugs and their delivery apparatus may play an important role in the reported incidences of catheter complications [6, 7]. Since silver alloys are commonly used in medical equipment, Mazzola *et al.* [1] studied the chemistry of 5-Fu in contact with silver, and found that contact with a high quality and pristine Ag(111) single crystal leads to degradation of 5-Fu and the release of HF. Although this provides useful indications of possible reactions, the pristine surface quality is unrepresentative of a real medical setting. Factors such as the crystal orientation and purity of a surface play a significant role for their catalytic activity [8]. In this work we show that, surprisingly, the efficiency of drug deterioration at body temperature is even higher for non-pristine silver surfaces than for pristine Ag(111). The silver surface used in this experiment is hospital grade: it is a polycrystalline medical alloy containing 95 % silver, and it has not undergone specialised surface preparation.

2. Expectations from theory

Before presenting our experimental findings, we introduce a computational approach using density functional theory (DFT). DFT is a powerful method which has been used to study tautomerisation of 5-Fu [9], inter-molecule attractions [10], and interactions between 5-Fu and nanoparticles [11, 12] and nanotubes [13]. Here we use DFT to examine the energetics of possible reaction pathways of 5-Fu on silver surfaces [See 'Methods' section for details].

First, we need to take into account the polycrystallinity of a real Ag surface: we can reasonably approximate such a surface as consisting of the three lowest energy cleavage planes, i.e.: the planes with Miller indices (111), (100) and (110). Our substrate model consists of 4 layers of Ag atoms and 2 nm vacuum in z direction. In Fig. 1(a) the calculated steps of the reaction are shown. In the figure, the substrate is Ag(100), but the reaction steps are very similar on Ag(111) and Ag(110). Step (i) involves the absorption of the molecule onto the surface with adsorption energies -1.00 eV, -1.43 eV, -0.99 eV for Ag(111), Ag(100) and Ag(110), respectively. These values indicate that 5-Fu weakly physisorbes on the substrate. In step (ii), the CF bond and a CH bond are broken, and H and F (not shown) are liberated from the molecule, but stay bound to the Ag surface. In steps (iii) and (iv), the reaction product is stabilised by a redistribution of the remaining

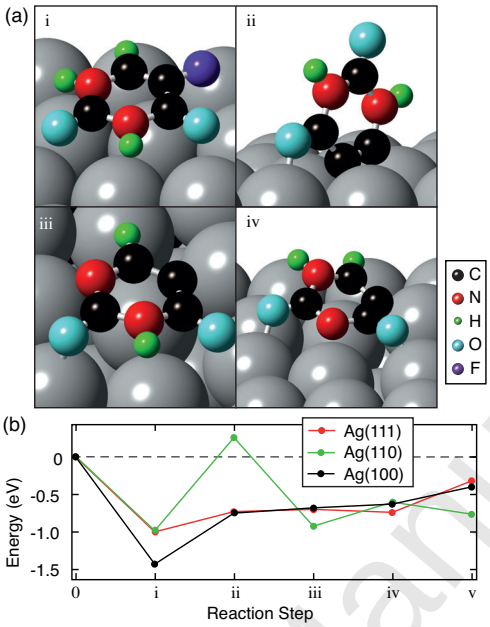

Figure 1: Energetics of the degradation process of 5-Fu on Ag. (a) i-iv Calculated reaction pathway of 5-Fu on Ag(100). (b) Energy diagram for the reaction between 5-Fu and Ag(111), Ag(110) and Ag(100).

H-atoms. Finally, in step (v) (not shown), the molecule remains unchanged, but the H and F recombine and desorb from the surface as HF. The energies of the products are -0.32 eV, -0.40 eV, -0.77 eV for Ag(111), Ag(100) and Ag(110), respectively. In Fig. 1(b), the corresponding energy diagram is shown. Although there are some differences in the energy of the intermediate steps, the reaction product is similarly favorable for all of the surfaces. These calculations thereby indicate that the polycrystallinity of a real surface is not of major importance, since all of the common surface orientations display similar catalytic activity with respect to the 5-Fu→HF reaction.

Whilst surface orientation appears to be less important for the degradation of 5-Fu on silver, surface cleanliness cannot be ignored: For all the surfaces studied, the most favourable mechanism relies on intermediate steps (ii-iv) in which H and F are temporarily bonded to the clean Ag surface – thus a lack of available active Ag sites (because of contamination) will hinder this pathway. We therefore investigate alternative reaction pathways in which these intermediate steps are not required. Several such pathways exist, but they involve more than one 5-Fu molecule; In the bulk crystal structure of 5-Fu, the molecule-molecule attraction is dominated by hydrogen bonding between an H atom of one molecule and the F atom of a neighbouring molecule [14] – and a similar ordering (and therefore H to F attraction) has been reported for thin films on Ag(111) [1]. It is therefore possible that the H to F attraction could lead to reactions between neighbouring 5-Fu molecules.

In order to investigate new reaction pathways, we have expanded the calculation to accommodate two 5-Fu molecules, and thus, possible reaction products now include dimerised 5-Fu. Dimerization has important implications in biological processes; for ex-

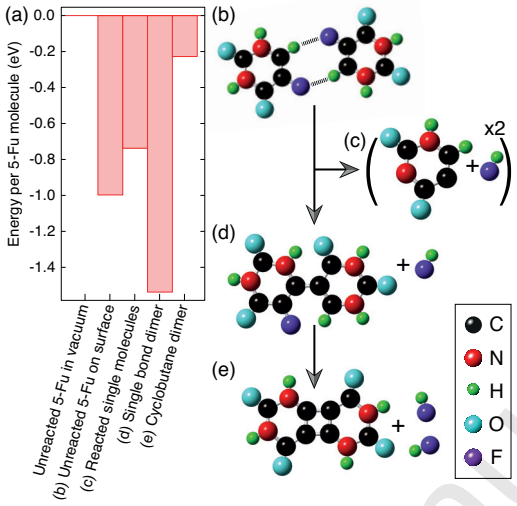

Figure 2: Energetics of possible reactions on an Ag surface. (a) Energy diagram (relative to $E \equiv 0$ for unreacted molecules in vacuum) of some possible products of two 5-Fu molecules. (b) two unreacted molecules absorbed on the surface, attracted by H:F bonding, (c) reacted individual molecules, (d) single-bonded dimer formation with the release of one HF molecule and (e) cyclobutane dimer formation with the release of two HF molecules. Note: the calculation is performed on a Ag(111) surface, and in each case, the molecules lie flat on the surface - i.e. the view in the figure is normal to the (111) surface.

ample dimerisation of thymine into cyclobutane pyrimidine is one of the central reactions generating melanoma [15]. Although cyclobutane pyrimidine is not a possible product here, closely related products (see Fig. 2 (e)) are conceivable.

The calculations reveal several stable products. The initial step of absorbing 5-Fu onto the surface releases around 1 eV per 5-Fu molecule (Fig. 2(b)). With a small energy difference, H and F atoms can be liberated from 5-Fu and evaporate as HF (Fig. 2(c)), giving the same reaction products as reported previously [1], with the same energy, but with the important difference that the intermediate steps (with H and F bonded to the Ag substrate) are not required. We also identify two dimer products; Fig. 2(d) shows a single bonded dimer and Fig. 2(e) shows that a second HF molecule can be released if the dimer forms a cyclobutane-linked product. By considering the energetics of these products (Fig. 2(a)), it is clear that the single bonded dimer is the most favourable, and that the cyclobutane dimer requires additional energy. From the calculations, we therefore understand that the monomer product (with a release of one HF molecule per 5-Fu molecule) and the single bonded dimer (with the release of one HF molecule per pair of 5-Fu molecules) are most favourable. These reactions do not require intermediate steps in which H and F are mobile on the Ag surface – and hence are less sensitive to surface contamination. Finally, we infer from the calculations that it is also possible to create an interesting cyclobutane product, but, as is the case with UV induced skin melanoma, this reaction requires an input of energy.

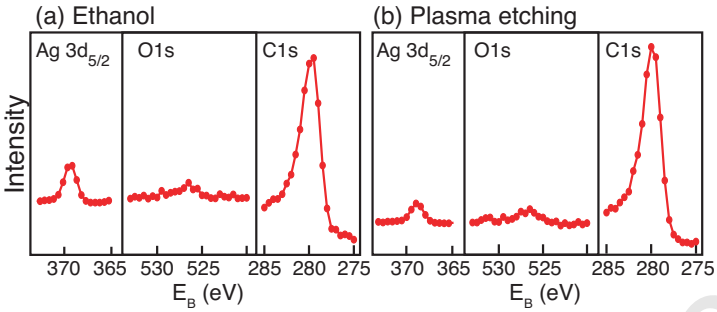

Figure 3: XPS measurements of the Ag $3d_{5/2}$, O1s and C1s core levels of polycrystalline Ag samples cleaned using (a) ethanol and (b) plasma etching. Here, the kinetic energies of the electrons are in the range 475 eV - 720 eV, corresponding to a mean free path of ≈0.5 nm. Quantitative analysis reveals the contamination thickness to be 2 nm for both samples, and to be ≈ 90% carbon and ≈ 10% oxygen.

3. Experimental

In addition to calculations, we also performed X-ray Photoelectron Spectroscopy (XPS) and X-ray Absorption Spectroscopy (XAS) measurements, using synchrotron radiation at beamline D1011 at the MAX II light source. Two silver samples were cut from a sheet of polycrystalline silver. One sample was cleaned by simply rinsing it with ethanol (as may be typical in a hospital) and the other was cleaned using oxygen plasma etching. The samples were mounted on the same sample holder, then heated to 500 °C in ultra high vacuum to remove weakly absorbed species such as water.

To monitor surface contamination, spectra were acquired from the nominally clean samples before depositing 5-Fu (Fig. 3). Quantitative analysis reveals that the main contaminants are carbon (≈ 90%) and oxygen (≈ 10%). Despite different cleaning routines, the quantity is similar in both cases: i.e. ≈ 2 nm (assuming uniform thickness).

After analysis of the nominally clean surfaces, 5-Fu was thermally evaporated onto the samples at low temperature (−170 °C), so as to prevent possible reactions by lowering the thermal energy available. The same samples were measured both at low temperature and after warming to body temperature.

In our measurements, the photon energy was chosen individually for each core level, such that the kinetic energy of the photoelectrons would be similar (≈ 160 eV), and thus a similar escape depth [16] (≈0.5 nm). The XPS data have undergone a Shirley-plus-linear background subtraction and each component of the core level has been fitted by a Voigt function. The number of components was chosen based on the stoichiometry of the 5-Fu molecule (F : N : C : O = 1 : 2 : 4 : 2), and on the basis of reducing χ^2 [17, 18]. All fitted components have the same full-width-at-half-maximum (FWHM), set equal to the smallest recorded FWHM for the samples (1.57 eV, based on the N1s peak at 38 °C, see Fig. 5(b)). The height and area of the components used to fit a single photoelectron peak are fixed to be the same (e.g. Fig. 4), which gives the best agreement between data and model. All data have undergone an intensity normalization to account for the beam current and the photoionisation cross-section [19, 20].

The deposition was carried out by thermally evaporating ≈ 4 nm of 5-Fu onto the Ag samples (see Fig. 4). Such a film thickness is large compared to the probing depth of XPS

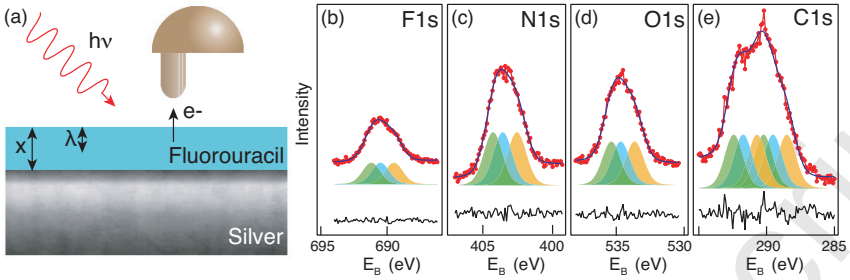

Figure 4: (a) Schematic of XPS of a bulk-like 5-Fu layer. X-rays absorbed by the sample result in emission of photoelectrons, which is limited by the mean free path ($\lambda \approx 0.5$ nm). Since the thickness x (≈ 4 nm) of the 5-Fu film is significantly larger than the mean free path, $x \gg \lambda$, the interface region is not probed. (b)–(e) XPS data containing photoelectron intensities of a bulk-like (unreacted) 5-Fu film with low molecule mobility ($T = -170\,^{\circ}$C) showing the 1s core levels of F, N, O and C. Raw data (red dots) with fit model (blue curve) containing multiple components with separations $\Delta E_{\text{green, blue}} \approx 0.7$ eV and $\Delta E_{\text{blue, orange}} \approx 1$ eV for all core levels, indicating an inhomogeneous deposition. Black traces depict the residuals (raw data minus fit model).

(≈ 0.5 nm), thus the spectral information can be considered 'bulk-like'. The data have been fitted with multiple components, which probably arise from inhomogeneity in the sample (for example, inhomogeneous surface interaction, such as charge transfer, leading to multiple core-level shifts) but has no affect on the stoichiometry analysis which relies only on the total peak area. From this procedure we find the stoichiometry of the 5-Fu layer to be $\mathrm{F:N:C:O} = 0.9 : 2 : 4.1 : 1.7$ (normalized to $\mathrm{N} \equiv 2$), in reasonable agreement with the expected stoichiometry of intact molecules, and measurements performed on pristine crystalline silver ($\mathrm{F:N:C:O} = 0.9 : 2 : 4.2 : 1.6$ [1]). This confirms that 5-Fu can be reproducibly thermally evaporated without disturbing the stoichiometry.

In order to understand the interaction at the silver surface, XPS measurements were also collected from a thinner 1 nm 5-Fu film (see Fig. 5). These results have been presented together with the data from 5-Fu on single crystal Ag(111) for comparison. Note that all core levels obtained from the 5-Fu thin film are shifted compared to the corresponding bulk measurements. This can be attributed to a charge transfer between the 5-Fu and the substrate, which results in an effective doping of the system and is not uncommon for organic/semiconducting thin films [21, 22]. The XPS data of Fig. 5(b) and Fig. 5(c), which correspond to 5-Fu on polycrystalline samples after ethanol cleaning and plasma etching, respectively, do not show significant differences. The samples, as mentioned previously, also have a similar level of surface contamination. Thus, hereafter, we only consider data from the sample cleaned with ethanol.

3.1. Degradation of 5-Fu on silver

The data acquisitions in Fig. 5(a), show signs of a chemical reaction between the 5-Fu and the pristine single crystal Ag substrate already at $-170\,^{\circ}$C, indicating that the thermal energy needed for such a reaction to take place is very small. This reaction was attributed to the transfer of an H-atom from one of the N-atoms which makes up the benzene-like ring to the Ag surface, and gives rise to an energy splitting (of ≈ 2.2 eV)

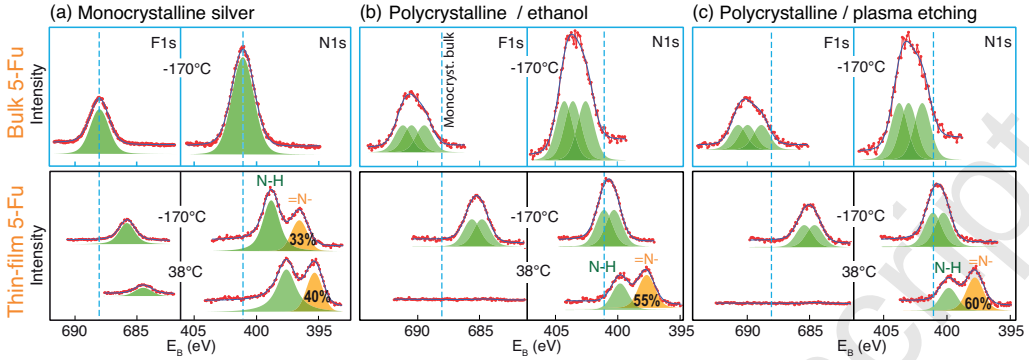

Figure 5: XPS measurements of the F1s and N1s core levels on (a) the monocrystalline Ag sample studied by Mazzola *et al.* [1], and the two polycrystalline Ag samples cleaned using (b) ethanol and (c) plasma etching (all peaks have been corrected for photoemission cross-section, measuring time and beam current). A model (blue curve) made from Voigt-shaped components (green) has been fitted to the data (red dots). The two rows show the bulk-like 5-Fu (film thickness ≈4 nm) (bulk-like; upper panels) and 1 nm (thin-film; lower panels). The dotted line shows the location of the bulk peak center for the monocrystalline sample. The similarity between the data from the two polycrystalline samples is in accordance with the similarity in contamination in Fig. 3. The relative size of the N1s components indicates that 80 % and 100 % of the 5-Fu molecules have reacted monocrystalline and polycrystalline samples, respectively.

of the N1s core level. Whilst at −170 °C no reaction is observed for the polycrystalline sample, at body temperature the N1s splits into two components, separated by 2.1 eV, indicating that a similar dehydrogenation of nitrogen has occurred. The different initial temperature needed for a reaction to occur suggests that the activation energy of this process is very different, hence a different pathway may be involved.

Although the N1s peak of 5-Fu on pristine Ag(111) suggests dehydrogenation at low temperature, a loss of F is *only* seen on warming to body temperature (Fig. 5(a) and Ref. [1]). This is consequence of the multi-step reaction pathway; at low temperatures, H and F can be liberated from 5-Fu, but remain bonded to the surface. Only with an increase in thermal energy can H and F recombine into HF and leave the surface. For the 5-Fu films on non-pristine polycrystalline samples (Fig. 5(b-c)) the dramatic loss of F is concomitant with the dehydrogenation of N, supporting the notion of a single step reaction to liberate HF. It is also interesting to note that the body temperature reaction is even stronger on non-pristine polycrystalline silver, compared to pristine Ag(111). The intensity ratio of the two N1s components is consistent with one N per 5-Fu being dehydrogenated, and the F1s signal is reduced below our detection limit (c.f. pristine Ag(111) in which ≈ 0.8 N atoms per 5-Fu are dehydrogenated and ≈ 80% of the F1s signal is lost). In other words, non-pristine surfaces have a higher energy barrier, but at body temperature 5-Fu degradation occurs with a very high efficiency. This interpretation is fully consistent with our DFT study; a pristine surface (Fig. 1(b) and Ref. [1]) lowers the activation energy by offering catalytic sites for temporary H and F bonding. When the surface is contaminated, then the same end product can be reached in a single step reaction due to H to F attraction between neighbouring 5-Fu molecules (Fig. 2). Although thermal energy is required for this process, body temperature is more than sufficient.

XAS also supports the aforementioned interpretation. Fig. 6 shows XAS data of the

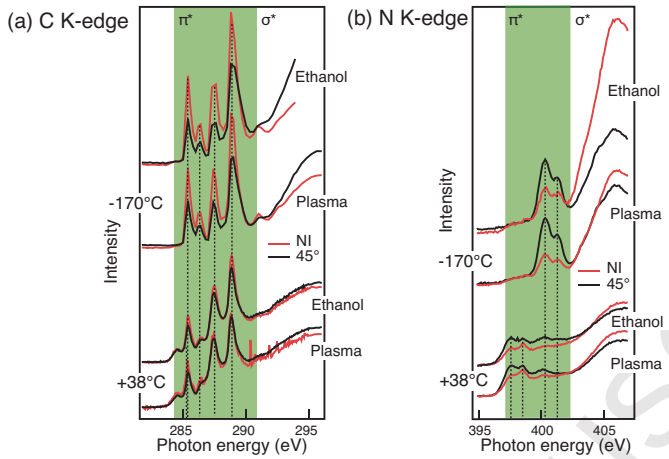

Figure 6: (a) XAS data showing the carbon K-edge for the 5-Fu thin film on the polycrystalline sample. Similar $\pi^\star$ structures are visible at $-170\,^\circ$C and $38\,^\circ$C, indicating an intact aromatic ring. (b) Nitrogen K-edge, where the appearance of additional structures at lower photon energy confirms the change in bond configurations for some nitrogen atoms.

C and N K-edge absorption acquired for the 5-Fu thin film on the two polycrystalline silver substrates. The carbon XAS data (Fig. 6(a)) show only a weak temperature dependence, except for the development of a structure at low photon energies, and at body temperature. Such a structure indicates that transitions involving the lowest unoccupied molecular orbital (LUMO) can occur with a lower excitation energy, indicating less occupied $\pi^\star$-states, consistent with the loss of F from the molecule. The existence of distinct $\pi^\star$-bonds at both temperatures shows that the delocalized $\pi^\star$-bonds remain, hence that the C and N ring is intact and that a cyclobutane ring has not formed. The N K-edge (Fig. 6(b)) is significantly modified with increasing temperature, and the appearance of two components located at lower photon energies at body temperature confirms that nitrogen has a modified bonding environment. The separation of these new components is similar to that of the original signal from N ($\sim$1 eV, indicated by vertical dotted lines), and could thus correspond to N atoms with new π bonding, due to the formation of a double bond in the aromatic ring, after releasing H.

3.2. Comparison with other metals

We have carried out analogous studies of 5-Fu on pristine Pt(111), and polycrystalline Pt and Cu (99.9%). The polycrystalline Pt and Cu samples were cleaned, and coated with 5-Fu in the same manner as for polycrystalline Ag; the data is presented as Fig. 7. Measurements performed on pristine Pt(111) (not shown) are extremely similar to polycrystalline Pt, we therefore infer that surface contamination is less important for Pt.

For both Cu and Pt, a loss of F1s is seen already at the lowest temperature, and becomes more pronounced as the temperature is increased. Around body temperature, the F : N ratio is 0.75 : 2 for Pt, and 0.50 : 2 for Cu (c.f. 1 : 2 for unreacted 5-Fu). Under similar conditions, the 5-Fu on Ag is fully reacted and has F:N = 0 : 2 (i.e. F1s is below our detection limit). Thus, on all three metals, fluorine has been released, but the loss is more dramatic in the case of Ag.

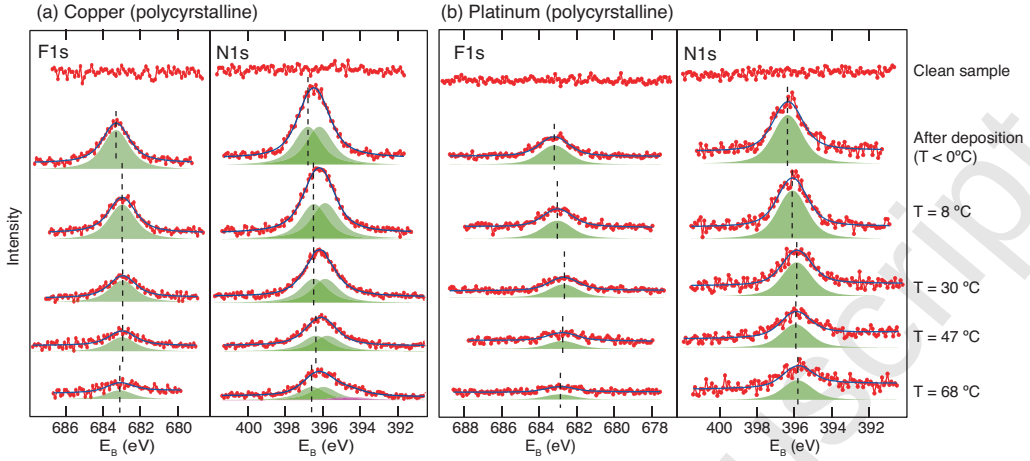

Figure 7: XPS measurements of 5-Fu on (a) polycrystalline Cu and (b) polycrystalline Pt ($h\nu = 1254$ eV). In both cases, both F1s and N1s are shown, and have been normalised for acquisition time and photoionisation cross-section. 5-Fu is deposited on a roughly cleaned surface at low temperature (copper: $\approx -10°$C, platinum $\approx -20°$C), then warmed to $\approx +68°$C. At all stages of the experiment, the F : N ratio is lower than the bulk stoichiomentry of 1 : 2, and the F deficiency becomes more pronounced as the temperature is increased. At 68°C, the ratio is reduced to 0.38 : 2 (Cu) and 0.52 : 2 (Pt). The data is shown as red markers, the fit envelope as a blue curve, and the fit components as green and purple shading. The small purple component identifies the component attributed to dehydrogenated N.

In the case of 5-Fu on Ag, a new N1s component (2.1 eV from the unreacted N1s) in concomitant with the loss of F. This component is due to the dehydrogenation of one of the N atoms in the molecule. Such a component is not seen for 5-Fu on Cu or Pt (except for a trace amount in at 68°C for Cu, marked in Fig. 7(a) in purple). In the case of Cu, a new component with a small energy splitting is seen, and for Pt, no new components are seen at all. We therefore speculate that the loss of F is not connected to dehydrogenation of an N atom, and that the F_2 (rather than HF) may be the main product. Note: the C1s and O1s core levels (not shown) also show no significant change during heating. Finally, our calculations suggest that the attachment of the 5-Fu molecule to the Cu surface involves one of the N atoms in the molecule, and the small core level shift of the new N1s component is consistent with such a bonding modification.

4. Discussion

DFT, XPS and XAS are consistent with the picture that 5-Fu readily degrades on metal surfaces. We observe a loss of F from 5-Fu in contact with Ag, Cu and Pt, with the reaction on Ag being the most vociferous. Surprisingly, the degradation of 5-Fu at body temperature is even more severe on non-pristine silver surfaces (compared to the already very reactive pristine Ag(111)). Our study shows that an alternative reaction pathway is invoked for carbon-coated Ag samples: The pathway for pristine Ag involves H and F being transferred from the 5-Fu molecule to the surface with little or no energy barrier, followed by H and F recombination (to form HF) on warming [1], for non-pristine samples, the lack of reactive silver surface sites prohibits this first step, and instead, a

single step reaction occurs in which F and H directly combine into HF and desorb from the sample. This single step process is consistent with the experimental observations: The presence of C species inhibits the intermediate steps in which F and H are mobile on the surface, but does not hinder the competing single step reaction pathway.

Our DFT study also indicates that dimer products are possible, however these are not observed experimentally. According to our calculations, the single-bonded dimer product is favourable, and would also involve the release of HF. On the other hand, this reaction releases only one HF molecule per two 5-Fu molecules, and would hence result in a 50% reduction of the F1s signal. Experimentally, we see a 100% loss of the F1s signal, and hence it is clear that this single-bonded dimer is not a common product. We comment that the final product is not only dictated by the energy, but, in the related case of UV damage to thymine, restrictions in orientiation and de-excitation of an excited intermediate may also play an important role [23].

Our calculations indicate that a cyclobutane-linked dimer product is also possible, but it is not observed experimentally. This is because it less energetically favourable than the other products. As with cyclobutane pyrimidine formation in skin melanoma, it may be possible to create the cyclobutane dimer product by exposure to a carefully selected UV wavelength, but more stable products are otherwise favoured.

5. Conclusion

In conclusion, our study shows that 5-Fu readily degrades on a range on metal surfaces, even when a realistic degree of surface contamination is present. In the case of Ag, the reaction is enhanced as the quality and cleanliness of the silver surface is reduced to that approximating real medical equipment. The intermediate reaction products during the degradation of 5-Fu appear to be different on monocrystalline and polycrystalline substrates, but the final product is the same in both cases and involves the formation of HF at body temperature. The fraction of reacted 5-Fu molecules indicates that the amount of HF produced by 5-Fu degradation could be even higher for non-pristine medical silver alloys than for a model surface. This indicates that the medical equipment itself may unintentionally alter the function of the drugs, and patients receiving 5-Fluorouracil may experience unintentional exposure to HF produced as a result of contact between 5-Fu and silver at room temperature. Our results indicate that care is required when selecting materials for the delivery of reactive drugs such as 5-Fu and that metal surfaces in general, and argentic surfaces in particular, raise concern.

Acknowledgments: This research was supported in part with computational resources at NTNU provided by NOTUR (project nn9331k). NP and DWB acknowledge The Research Council of Norway for the financial support through M-ERA.NET project RADESOL under the European Unions seventh framework programme (FP/2007-2013), grant agreement no. 234648/O70.

Methods: All calculations were performed using the Quantum Espresso package [24] with generalized gradient approximations (GGA) with Perdew-Burke-Ernzerhof exchange-correleation functional [25] and ultra soft pseudo-potentials [26]. The GGA method was used because it employs more sophisticated approximations to the exchange-correlation

energy than the Local Density Approximation (and LDA+U), thus offering more accurate results. A van der Waals correction, using the Grimme 2D approximation [27], was also taken into account. We employed cutoffs of 70 Ry on the plane wave and 700 Ry on the electronic density. Only the Γ point was used for the k-point sampling of the Brillouin-zone. This setup was verified to obtain satisfactory accuracy for the Ag bulk and surfaces[1].

[1] F. Mazzola, T. Trinh, S. Cooil, E. R. Østli, K. Høydalsvik, E. T. B. Skjønsfjell, S. Kjelsrup, A. Preobrajenski, A. A. Cafolla, D. A. Evans, D. W. Breiby, and J. W. Wells, 2D Materials **2**, 025004 (2015).

[2] B. W. Stewart and C. P. Wild, eds., *World Cancer Report 2014* (International Agency for Research on Cancer, World Health Organization, 2014).

[3] The American Cancer Society, "Central venous catheters," `http://www.cancer.org/treatment/treatmentsandsideeffects/treatmenttypes/chemotherapy/central-venous-catheters` (2014), [Online; accessed February 12, 2015].

[4] N. P. O'Grady, M. Alexander, L. A. Burns, E. P. Dellinger, J. Garland, S. O. Heard, P. A. Lipsett, H. Masur, L. A. Mermel, M. L. Pearson, I. I. Raad, A. G. Randolph, M. E. Rupp, and S. Saint, Clinical Infectious Diseases **52**, E162 (2011).

[5] M. O. Almeida, D. A. S. Barros, S. C. Araujo, S. H. D. M. Faria, V. G. Maltarollo, and K. M. Honorio, Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy **184**, 169 (2017).

[6] B. Ardalan and M. R. Flores, Cancer **75**, 2165 (1995).

[7] A. H. Verhage and E. F. H. van Bommel, Nephrology Dialysis Transplantation **15**, 901 (2000).

[8] Y. Nishiyama and H. Wise, Journal of Catalysis **32**, 50 (1974).

[9] A. Yaraghi, O. M. Ozkendir, and M. Mirzaei, Superlattices and Microstructures **85**, 784 (2015).

[10] M. Mirzaei, O. Gülseren, and N. Hadipour, Computational and Theoretical Chemistry **1090**, 67 (2016).

[11] A. Kouchaki, O. Gülseren, N. Hadipour, and M. Mirzaei, Physics Letters A **380**, 2160 (2016).

[12] M. B. Javan, A. Soltani, Z. Azmoodeh, N. Abdolahi, and N. Gholami, RSC Adv. **6**, 104513 (2016).

[13] A. Soltani, M. T. Baei, E. Tazikeh Lemeski, S. Kaveh, and H. Balakheyli, Journal of Physics and Chemistry of Solids **86**, 57 (2015).

[14] A. T. Hulme, S. L. Price, and D. A. Tocher, *Journal of the American Chemical Society*, Journal of the American Chemical Society **127**, 1116 (2005).

[15] S. E. Freeman, H. Hacham, R. W. Gange, D. J. Maytum, J. C. Sutherland, and B. M. Sutherland, Proceedings of the National Academy of Sciences of the United States of America **86**, 5605 (1989).

[16] M. P. Seah and W. A. Dench, Surface and Interface Analysis **1**, 2 (1979).

[17] R. Andrae, T. Schulze-Hartung, and P. Melchior, "Dos and don'ts of reducing chi-squared," (2010), arXiv:1012.3754 .

[18] R. Andrae, "Error estimation in astronomy: A guide," (2010), arXiv:1009.2755 .

[19] J. J. Yeh and I. Lindau, Atomic Data and Nuclear Data Tables **32**, 1 (1985).

[20] Elettra Sincrotrone Trieste, "Atomic calculation of photoionization cross-sections and asymmetry parameters," `https://vuo.elettra.eu/services/elements/WebElements.html` (1993), [Online; accessed April 24, 2015].

[21] G. Cabailh, J. W. Wells, I. T. McGovern, V. R. Dhanak, A. R. Vearey-Roberts, A. Bushell, and D. A. Evans, J. Phys. Cond Matt. **15**, S2741 (2003).

[22] F. Song, J. W. Wells, K. Handrup, Z. S. Li, S. N. Bao, K. Schulte, M. Ahola-Tuomi, L. C. Mayor, J. C. Swarbrick, E. W. Perkins, L. Gammelgaard, and P. Hofmann, Nature Nanotechnology **4**, 373 (2009).

[23] J. Vinje, M. Falck, F. Mazzola, S. Cooil, H. Koch, I.-M. Høyvik, and J. Wells, Langmuir (in press) (2017).

[24] P. Giannozzi, S. Baroni, N. Bonini, M. Calandra, R. Car, C. Cavazzoni, D. Ceresoli, G. L. Chiarotti, M. Cococcioni, I. Dabo, *et al.*, Journal of physics: Condensed matter **21**, 395502 (2009).

[25] J. P. Perdew, K. Burke, and M. Ernzerhof, Physical review letters **77**, 3865 (1996).

[26] A. M. Rappe, K. M. Rabe, E. Kaxiras, and J. Joannopoulos, Physical Review B **41**, 1227 (1990).

[27] S. Grimme, Journal of computational chemistry **27**, 1787 (2006).